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Liver Friendly GERD Management

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Abstract:- Gastro Esophageal Reflux Disease (GERD) is a common experienced upper (Gastro Intestinal Tract)GIT disease in world, specially for third world country. for remedy people used to take medications like Proton Pump Inhibitor (PPI) ,acid neutralizers and so on.as different anti ulcerant use metabolic co enzyme for there activation.As liver is the main site for metabolism in body for various substance,safe liver friendly anti ulcerant is a burning issue for proper management of Gastro Intestinal Tract (GIT) diseases.People are generally unware of this case but a moderate awareness and practice help a greater mass for protecting themselves from drug induced liver disease.Here the article is based on that kind of short discuss about liver suitable GERD management.

I. INTRODUCTION

Approximately a certain percentage of general population take a proton pump inhibitor (PPI) drug to block stomach acid secretions and relieve symptoms of frequent heartburn, acid reflux and gastroesophageal reflux disease. That percentage can be as much as seven times higher for people with chronic liver disease. PPIs, which include different types of brand name most commonly prescribed medications in the world, particularly among people with chronic liver disease. To determine the effect of gastric acid suppression on the progression of chronic liver disease, researchers observed alcoholic liver disease, Non Alcoholic Fatty Liver Disease (NAFLD) and Non Alcoholic Steato Hepatitis (NASH) in humans. In each, they blocked gastric acid production either by genetic engineering or with a PPI .

II. PATHOPHYSIOLOGY

Proton pump inhibitor use increases the risk of developing alcoholic liver disease among alcohol-dependent patients. Reduction of gastric acid secretion therefore appears to promote overgrowth of intestinal Enterococcus, which promotes liver disease, based on data from mouse models and humans.

A. CLINICAL FEATURES

- Weakness
- Poor appetite
- Dark urine
- Icteric sclera patients
- Yellowed skin
- Abdominal pain

B. Mechanism Of PPI:

The proton pump inhibitors (PPIs) (mainly Omeprazole & Esomeprazole) are the most potent suppressants of gastric acid secretion available and are used widely in the therapy of gastroesophageal reflux and peptic ulcer disease. PPIs are prodrugs that require gastric acid for their activation. After absorption they diffuse into the parietal cells of the stomach and accumulate in the acidic secretory canaliculi. The activated form of the PPIs binds covalently to the H+/K+-ATPase of the acid-producing parietal cell, inactivating the pump molecule that transports protons (H+ molecules) into the gastric lumen.Liver biopsy typically shows prominent centrolobular necrosis, suggestive of an acute, toxic hepatic injury (acute hepatic necrosis);however, recurrence upon rechallenge has been documented in several cases.

Likelihood Score-B (rare but likely cause of clinical apperant injury).

C. MECHANISM OF INJURY:

The acute onset and rapid recurrence of hepatic injury with omeprazole and esomeprazole suggests a hypersensitivity reaction, but may merely reflect altered metabolism or acute toxicity of a metabolic byproduct. The usual clinical phenotype is acute hepatic necrosis. Both omeprazole and esomeprazole are extensively metabolized by the hepatic P450 system and have multiple effects on the drug metabolizing system, including inhibition of CYP 2C19 and induction of CYP1A2, effects which may cause significant drug-drug interactions.

D. OUTCOME AND MANAGEMENT:

- Mild and Asymptomatic.
- Elevated Serum aminotransferase.
- Clinically apparent injury calls for prompt withdrwal.
- Acute liver failure due to Omeprazole and Esomeprazole is rare but some degree of reactivity may be happened due to there Benzimidazole structure.

➢ Key Points:

Medication:	Omeprazole &Omeprazole(20 mg daily)
Pattern:	Hepatocellular (R=100)
Severity:	5+ (acute liver failure and death)
Latency:	14 days to onset of symptom
Recovery:	None
Other medications:	Atenolol, diltiazem and aspirin chronically, ranitidine for 10 days immediately before omeprazole was started

E. HEPATOTOXICITY OF PPI:

- Pantoprazole-
  - In case of large scales and long term trial
  - Serum ALT elevations have occurred in less than 1% of patients
  - Clinical apparent liver diseases are rare as well as some hepatic necrosis are being found with other PPIs.
  - Injury arises first 4 weeks of therapy.
  - Likelihood Score- C (probable rare cause of clinically apparent liver injury).

- Key Points:

Medication	Pantoprazole(not given)
Pattern	Hepatocellular (R=37)
Severity	3+,(jaundice, Hospitalization)
Latency	8 days to onset of symptoms, 9 days to jaundice
Recovery	~ 2 weeks
Other Medication	Intravenous Midazolam 3 days before Onset

- Laboratory Values:

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L	Bilirubin (mg/dL)	Other
5 days	0	12	13		Upper endoscopy
8 days	0	359	175	1.0	Epigastric pain
9 days	1 day	590	190	3.5	Jaundice
10 days	2 days	555	180	2.5	
12 days	4 days	310	170	0.6	
17 days	9 days	100	100	0.5	Discharged
Normal Values		<17	<130	<1.2	

F. Lansoprazole and Dexlansoprazole-

- In case of large scales and long term trial
- Serum ALT elevations have occurred in less than 1% of patients
- The time to onset was within 2 to 4 weeks and the pattern of enzyme elevations was hepatocellular or mixed.
- Hypersensitivity reactions with fever, rash and eosinophilia have been described associated with DRESS (Drug-rash with eosinophilia and systemic symptoms)
- Likelihood Score- C (probable rare cause of clinically apparent liver injury).

G. MECHANISM OF INJURY:

Several features of the hepatic injury with Lansoprazole suggest a hypersensitivity reaction, but may merely reflect altered metabolism or acute toxicity of a metabolic byproduct. Lansoprazole is metabolized by the hepatic P450 system, but has little effect on the activity of the drug-metabolizing enzymes.

H. OUTCOME AND MANAGEMENT:

- Mild and Asymptomatic.
- Elevated Serum aminotransferase.
- Clinically apparent injury calls for prompt withdrwal.
- Acute liver failure due to Omeprazole and Esomeprazole is rare but some degree of reactivity may be happened due to there Benzimidazole structure.

- Key Points:

Medication:	Lansoprazole (30 mg daily)
Pattern:	Hepatocellular (R=~12.5)
everity:	3+ (jaundice, hospitalization
Latency:	25 days
Recovery:	50 days
Other medications:	None mentioned

I. Rabeprazole

- In case of large scales and long term trial
- Serum ALT elevations have occurred in less than 1% of patients
- The time to onset was within 4 weeks and the pattern of enzyme elevations was hepatocellular or mixed.
- Likelihood Score- D (possible rare cause of clinically apparent liver injury).

J. MECHANISM OF INJURY:

The acute onset and rapid recurrence of hepatic injury with proton pump inhibitors suggests a hypersensitivity reaction, but may merely reflect altered metabolism or acute toxicity of a metabolic byproduct. Rabeprazole is metabolized predominantly by the CYP 2C19 microsomal drug-metabolizing enzyme andmay interfere with clearance of other agents metabolized in a similar fashion.

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K. OUTCOME AND MANAGEMENT:

- Mild and Asymptomatic.
- Elevated Serum aminotransferase.
- Clinically apparent injury calls for prompt withdrwal.
- Acute liver failure due to Omeprazole and Esomeprazole is rare but some degree of reactivity may be happened due to there Benzimidazole structure.

III. COMPARASION AMONG DIFFERENT LIVER HEALTHY PPI

- **According to Likelihood score:** 5-point scale [A to E] that estimates whether a medication is a of cause liver injury: A=Well known cause; B=Highly likely cause; C=Probable cause; D=Possible cause; E=Unlikely cause; E*=Suspected but unproven cause; X=Unknown.

From previous discussion, we have seen

- For Omeprazole and Esomeprazole- Likelihood Score-B
- For Pantoprazole- Likelihood Score-C
- For Lansoprazole and Dexlansoprazole - Likelihood Score-C
- For Rabeprazole- Likelihood Score-D

So, we can chronologically arranged PPIs according to Likelihood Score

Rabeprazole> Pantoprazole/Lansoprazole/Dexlansoprazole> Omeprazole/ Esomeprazole.

According to different research, H2 receptor antagonist have better efficacy and safety in case of GERD management with liver diseases.

Antibiotic should be used according to clinical management and research.

Mechanism of Histamine Type 2(H2) Receptor Blocker:

The H2 blockers(Cimetidine, Ranitidine, Famotidine, Nizatidine) are specific antagonists of the histamine type 2 receptor, which is found on the basolateral (antiluminal) membrane of gastric parietal cells. The binding of cimetidine to the H2 receptor results in inhibition of acid production and secretion, and improvement in symptoms and signs of acid-peptic disease. The H2 blockers inhibit an early, "upstream" step in gastric acid production and are less potent that the proton pump inhibitors, which inhibit the final common step in acid secretion. Nevertheless, the H2 blockers inhibit 24 hour gastric acid production by about 70% and are most effective in blocking basal and nocturnal acid production. Metabolized by and can inhibit several isoforms of the hepatic cytochrome P450 system (CYP 1A2, 2C9 and 2D6), which can result in significant drug-drug interactions if administered with agents that rely upon their metabolism by these microsomal enzymes (such as digoxin, warfarin, oral contraceptives, isoniazid and phenytoin).

- Key point:

- Hepatotoxicity of Cimetidine:
  - Chronic Cimetidine administration causes minor elevation of Serum aminotransferase level in 1-4% of patients (similar result find in case of placebo recipents.)
  - Elevation of Alanine Aminotransferase (ALT) is usually asymptomatic and resolve with doses modification.
  - At least 7 months needed for onset of gross injury and within 4 to 12 weeks it resolves if Famotidine administration stopped.

- Likelihood Score:
  B (highly likely cause of clinically apparent liver injury)

- Mechanism of Injury:
  Cimetidine is metabolized by and inhibits the function of the microsomal P450 drug metabolizing enzymes, and injury may be the result of its activation to a toxic intermediate. Rapid recurrence with rechallenge is typical, but features of hypersensitivity are uncommon.

- Outcome and Management:

  - The hepatic injury caused by cimetidine is usually rapidly reversible with stopping the medication.
  - Cimetidine has not been definitively linked to cases of acute liver failure, but there has been at least one case of prolonged cholestasis with probable vanishing bile duct syndrome after an episode of cholestatic hepatitis attributed to cimetidine.

- Hepatotoxicity of Famotidine:
  - Chronic therapy with famotidine has been associated with minor elevations in serum aminotransferase levels in 1% to 4% of patients, but similar rates were reported in placebo recipients.
  - The ALT elevations are usually asymptomatic and transient, and may resolve without dose modification.
  - Onset has ranged from 1 to 14 weeks and serum enzyme pattern has typically been hepatocellular. The injury resolves within 4 to 12 weeks of stopping famotidine.

Likelihood score: C (probable rare cause of clinically apparent liver injury).

Medication	Famotidine
Pattern	Hepatocellular
Severity	3+ (jaundice,Hospitalization)
Latency	1 week
Recovery	5 week
Other Medication	Acetaaminophen (~ 2.5 g daily)

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- Laboratory Results:

Time After starting	Time after stopping	ALT U/L	ALK P U/L	Bilirubin mg/dl	other
pre		34	67	0.9	
7 days	0	305	182	7.1	Admission
8 days	1 day	250	162	6.7	
10 days	3 days	168	130	2.7	
16 days	9 days	69	88	1.3	
5 weeks	4 weeks	26	61	1.1	
Normal values		<25	<90	<1.2	

- Ranitidine:
  Use had been restricted under supervision of USFDA (United States Food and Drug Administration) in 2020 due to different kind organ and function impairement involvement.

- Hepatotoxicity of Nizatidine:
  - minor elevations in serum amino transfer as e levels in 1% to 4% of patients, but similar rates have been reported in placebo recipients.
  - The ALT elevations are usually asymptomatic and transient and may resolve without dose modification.
  - More information is available on the hepatotoxicity of other H2 blockers such as ranitidine and cimetidine which have been implicated in causing clinically apparent liver injury in 1:20,000 to 1:100,000 users.
  - The time to onset of H2 blocker induced liver injury tends to be short, between 1 and 6 weeks of starting, 4 to 12 weeks for resolving.

- Likelihood score: D (possible rare cause of clinically apparent liver injury).

- Mechanism of Injury:
  Nizatidine is metabolized by the microsomal P450 drug metabolizing enzymes and injury may be the result of its activation to a toxic intermediate. Despite its metabolism by the P450 system, nizatidine does not result in significant inhibitor or induction of the enzymes and thus is less likely to cause drug-drug interactions than cimetidine.

- Outcome and Management:
  - The hepatic injury caused by nizatidine is usually rapidly reversible with stopping the medication.
  - Nizatidine has been in use for a shorter time than cimetidine or ranitidine and remains unknown whether there is cross reactivity in hepatic injury between nizatidine and other H2 blockers.

- Key Points:

Medication	Nizatidine (not provided)
Pattern	Hepatocellular
Severity	Jaundice and other hepatocellular signs
Latency	2 weeks needed to appear jaundice and 8 weeks to need for laboratory confirmation
Recovery	Incomplete
Other Medications	Not mentioned

- Laboratory Values:

Time After Starting	Time After Slopping	ALT U/L	ALK P U/L	Bilirubin Mg/dl	Other
		Nizatidine is given for 4 weeks			
2 months	1 month	461	152	21.7	Protime 18.7 seconds
3.5 months	2.5months	255	168	16.8	Protime 20 sec
4 months	3 months	270	202	16.6	Biopsy massive necrosis
5 months	4 months	258	256	26.2	Discharge
12 months	11 months	74	252	1.8	Protime 13.4 sec
16 months	15 months				Biopsy cirrhosis
Normal Values		<40	<115	<1.2	

- Safety Efficacy and Comparison of Different H2 Blockers:
  According to livelihood score measurement we can rearrange H2 blockers chronologically according to safety and efficacy during different hepatic issues

  Nizatidine > Famotidine> Cimetidine. (Due to US-FDA restriction ranitidine is not mentioned in comparison)

- Role of Acid Neutralizers:
  A new study found that blocking stomach acid can lead to an overgrowth of intestinal bacteria that likely contributes

to liver inflammation and damage. The findings suggest that some widely used acid reflux (heartburn) medications may worsen chronic liver disease.

IV. CONCLUSION

Management of GERD is a common procedure with combination of OTC/ Prescribed drug and modified lifestyle.But in following prescribed drug, safety and efficacy should be ensured for good hepatic intact function to reduce the the risk of anti GERD drugs induced hepatic disease. Different research denotes long time Proton Pump Inhibitor (PPI) cause different liver diseases whereas in contrary to Histamine type 2 blockers are better option for management.More research and trials can ensure to avoid minimal adverse effect for GERD management.

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